REMARKS/ARGUMENTS

I. Status of the Claims

Claims 32-42 and 44-61 are pending in this application.

Claims 32-49 are rejected under 35 U.S.C. §112, first paragraph for allegedly failing to comply with the written description requirement.

Claims 50-61 are rejected under 35 U.S.C. §112, first paragraph for allegedly being incomplete for omitting essential elements.

Claims 32-42 and 44-49 are rejected under 35 U.S.C. §112, second paragraph for allegedly being indefinite. The rejection states that the claims fail to point out and distinctly claim the subject matter the Applicant regard as the invention.

II. Amendments to the Claims

Claims 33-47 and 49 are amended to designate the displayed structure as a "probe nucleic acid". Thus, the claim language is amended to comport with that of the corresponding independent claim 32.

Claims 50 and 57 are amended to designate the displayed structure as a "probe nucleic acid" and further to clarify that when the stabilizing moieties interact to bring the energy donor and acceptor into operative proximity, the probe nucleic acid "is not hybridized to a target nucleic acid."

Claims 52-56 and 58-61 are amended to comport the claim language with that of the corresponding independent claims.

III. Support for Amendments to the Claims

Support for the amendments to claims 33-47 and 49 and to claims 52-56 and 58-61 is found in previously presented claim 32, and as discussed below for claims 50 and 57. No new matter is added.

Support for the amendment to claims 50 and 57 is found in the specification at, for example, **FIG. 4** wherein a schematic shows the unhybridized probe with the stabilizing moieties (C) bringing the donor (Fluorophore, F) and acceptor (Quencher, Q) into operative proximity. The figure shows the probe hybridized to a target nucleic acid, resulting in the separation of the donor and acceptor. Additional support is found in the examples which describe a selected probe that is both unhybridized and hybridized to a target sequence. In particular, page 55, lines 30-31 states "[t]he difference in fluorescence output of each probe with and without a complementary hybridization target was compared." Upon hybridization of the probe with its target, the stabilizing moieties separate, forcing the donor and acceptor and out of operative proximity and producing fluorescence. Thus, the specification describes a probe which, in its unhybridized state, includes a donor and acceptor that are brought into operative proximity by the interaction of the stabilizing moieties. No new matter is added.

IV. Response to Claim Rejections

Under 35 U.S.C §112, First Paragraph

The Examiner rejects claims 32-49 as allegedly failing to comply with the written description requirement. In particular, the Examiner alleges that the claims contain subject matter that was not described in the specification in such a way as to reasonably convey that, at the time the application was filed, Applicant had possession of the claimed invention. In this context, the Examiner refers back to the rejection issued in the Office action of October 15, 2003.

According to the May 16, 2005 Office action, it appears that there are three aspects to the written description rejection, namely: (1) that there allegedly is no support in the specification for a linker moiety which links the non-nucleic acid stabilizing moiety to the molecular energy transfer donor and/or the molecular energy transfer acceptor; (2) that there is allegedly no support in the specification for stabilizing moieties other than the specific CHOL moiety recited in claim 50; and (3) that the Applicant allegedly has not set any limits as to what non-nucleic acid stabilizing groups are fairly encompassed by the claims.

Unfortunately, it also appears from the record that the Examiner's concerns were not fully addressed in the response to the Office action of October 15, 2003, which was mailed by the Applicant's representative on January 30, 2004. Therefore, the issues raised in the Office action of October 15, 2003 are addressed herein.

(1) There is support for a linker moiety which links the non-nucleic acid stabilizing moiety to the molecular energy transfer donor and/or the molecular energy transfer acceptor

In the Office Action dated May 15, 2005, at the bottom of page 3, the Examiner alleges based upon the structures recited in original claim 32, that the structures X and Y (which represent stabilizing moieties) are limited to wherein X is *directly linked* to R (a molecular energy transfer donor), and/or A (a nucleic acid), and Y is *directly linked* to Q (a molecular energy acceptor), and/or A. The Examiner asserts (on page 4, second paragraph) that: "There is no support in the specification as filed or in the original claims for limiting the attachment of all forms of non-nucleic acid stabilizing moieties to the compounds of the invention via a linker moiety, wherein the linker served to link a phosphate group with nucleoside or nucleotide residues, and further wherein said nucleoside or nucleotide residues are linked to another linker that is attached to either a molecular donor or acceptor." Thus, it appears that the Examiner is objecting to the inclusion of the linker moiety in the structure because there is allegedly no support for such a linker.

As discussed in the teleconference of July 29, 2005, the specification provides ample support for a linker moiety which links the stabilizing moieties, X and Y, to the probe nucleic acid. Specifically, on page 25 of the specification, beginning at line 25, Applicant discloses that "linker groups" are "constituents of CAPs that link stabilizing moieties, donor and/or acceptor moieties and other groups to the oligonucleotide component of the CAP. The linker groups can be hydrophilic (*e.g.*, polyethylene glycol) or they can be hydrophobic (*e.g.*, hexane, decane, etc.)." Furthermore, on page 25, at line 30, continuing onto page 26, the specification recites that:

> In certain embodiments, it is advantageous to have a stabilizing moiety or other component of the CAP attached to the oligonucleotide component by a group that provides

flexibility and distance from the oligonucleotide. In this embodiment, the group to which the stabilizing moiety is bound is referred to as a "linker group" or "spacer."...

In an exemplary embodiment, the spacer serves to distance the reactive group and/or stabilizing moiety from the oligonucleotide. Spacers with this characteristic have several uses. For example, a stabilizing moiety held too closely to the oligonucleotide may not interact with its complementary group, or it may interact with too low of an affinity. When a stabilizing moiety is itself sterically demanding, the reaction leading to stabilizing moiety-complementary group interaction can be undesirably weakened, or it may not occur at all, due to a sterically-induced hindering of the approach of the two components.

In yet a further embodiment, the linker group is provided with a group that can be cleaved to release a stabilizing moiety, minor groove binder, intercalating moiety and/or acceptor moiety from the oligonucleotide. Many cleaveable groups are known in the art ... Moreover a broad range of cleavable, bifunctional (both homo- and hetero-bifunctional) linker groups are commercially available from suppliers such as Pierce.

Exemplary cleavable moieties can be cleaved using light, heat or reagents such as thiols, hydroxylamine, bases, periodate and the like. Preferred cleaveable groups comprise a cleaveable moiety which is a member selected from the group consisting of disulfide, ester, imide, carbonate, nitrobenzyl, phenacyl and benzoin groups.

Thus, linker groups as recited by the claims are fully supported in the specification.

(2) There is ample support in the specification for stabilizing moieties other than the specific CHOL moiety recited in claim 50

The Examiner alleges on page 4 of the Office Action that: "There are no teachings that suggest the structure disclosed in original claim 50 can or should be modified by replacing the CHOL moiety with the full scope of non-nucleic acid stabilizing moieties encompassed by the claimed invention as described on pages 17-20 of the specification as filed."

On page 6 of the Office Action, the Examiner alleges that: "The specification does not provide evidence of the interchangeability of CHOL in the specific context of the structure set forth in page 12 of the specification with any and every conceivable stabilizing group known in the art or described on pages 17-20 of the specification as filed."

As presented by the Applicant's representative during the teleconference of July 29, 2005, the specification does in fact support the inclusion of stabilizing groups other than CHOL.

Support for the teaching of stabilizing moieties other than CHOL can be found in the specification on for example, page 12, line 6 wherein it is stated that: "In contrast to previous probes, the CAPs of the invention utilize, for example, a hydrophobic-hydrophobic interaction between two or more stabilizing moieties to bring the donor and the acceptor into proximity."

The largest single segment of support for stabilizing moieties is found on pages 17 through 20 of the specification. In particular, starting at line 14 on page 17, the specification recites:

> ... The stabilizing moiety can induce the transient conformation using either attractive or repulsive forces. For example, a stabilizing group that repels another component of the CAP can be used to force the donor and acceptor proximate to each other. Exemplary repulsive mechanisms include, but are not limited to, incompatible steric characteristics, charge-charge repulsion, hydrophilic-hydrophobic interactions and the like.
>
> **In a preferred embodiment, the transient conformation is induced by an attractive mechanism between the stabilizing moiety and another component of the CAP. Exemplary attractive forces include, ionic bonding, ion pairing, van der Waals association, hydrophobic-hydrophobic interactions, complexation and host-guest mechanisms. In a preferred embodiment, stabilizing agents will interact by a hydrophobic-hydrophobic mechanism and X and Y are both hydrophobic moieties.** In a still further preferred embodiment, ***X and Y are members independently selected from*** saturated hydrocarbons, unsaturated hydrocarbons, ***steroids***, fatty acids, fatty alcohols and hydrophobic peptides...
>
> **Stabilizing moieties can also be selected from a wide range of small organic molecules, organic functional groups (*e.g.*, amines, carbonyls, carboxylates, *etc.*), biomolecules, metals, metal chelates and organometallic compounds.**
>
> When the stabilizing moiety is an amine, ... the stabilizing moiety will interact with a component of the CAP (*e.g.*, carboxyl groups, phosphate groups) that is complementary to (*e.g.*, complexing, ion-pairing) with the amine... (page 18, lines 4-7)
>
> In certain preferred embodiments, when the stabilizing moiety is a carboxylic, or other acid, the stabilizing moiety will interact with a component of the CAP by, for example, complexation (*e.g.*, metal ions) or ion-pairing (*e.g.*, quaternary ammonium cations)... (page 18, lines 9-12)

When the stabilizing moiety is a chelating agent, crown ether or cyclodextrin, host-guest chemistry will preferably dominate the interaction between the stabilizing moiety and the complementary component of the CAP. (page 18, lines 14-16)

In a particularly preferred embodiment, the stabilizing moiety is a cyclodextrin or modified cyclodextrin. (page 18, lines 27-28)

In another exemplary embodiment, the stabilizing moiety is a polyaminocarboxylate chelating agent such as ethylenediaminetetraacetic acid (EDTA) or diethylenetriaminepentaacetic acid (DTPA). In a preferred embodiment, this stabilizing moiety is attached to an amine-containing component of a CAP or a linker group attached to the CAP, for example, by utilizing a commercially available anhydride (Aldrich Chemical Co., Milwaukee, WI). This stabilizing moiety, in preferred embodiments will interact with a coordinatively unsaturated metal ion that is attached to the CAP by means of, for example, a second chelating agent. (page 19, lines 3-10)

In still further preferred embodiments, the stabilizing moiety is a biomolecule such as a protein, nucleic acid, peptide or an antibody. (page 19, lines 16-17)

In those embodiments wherein the stabilizing moiety is a protein or antibody, the protein can be tethered directly to a CAP component or via a linker group through any reactive peptide residue available on the surface of the protein. (page 19, lines 28-30)

Thus, the specification provides ample written description for quite a number of different stabilizing moieties, among them steroids, generally.

(3) Applicant recites specific limits as to what non-nucleic acid stabilizing groups are fairly encompassed by the claims

In response to the Applicant's earlier reference to *In re Wertheim*, on page 6 of the Office Action, the Examiner alleges that: "Applicant wishes to modify a specific structure by broadening the scope of the structure, such that the specific stabilizing group CHOL, is replaced with *any* non-nucleic acid stabilizing group. It is the Examiner's opinion that... Based upon the decision in *In re Wertheim*, broadening the scope of the claims to encompass a limitation where there is no upper limit constituted new matter."

However, as is clear from the specification, not just any molecule as disclosed above can function as a non-nucleic acid stabilizing moiety according to the invention. Indeed, as noted above, and as discussed in the teleconference of July 29, 2005, there are measurable

limits which define what exactly constitutes a stabilizing moiety suitable for the practice of the invention. Specifically, on page 13 lines 16-22, the specification recites:

> In choosing stabilizing moieties, any two groups that exhibit an affinity for each other can be used to bring the donor and acceptor into the desired proximity. **Presently preferred *stabilizing moieties are those that meet four criteria*: (1) *the binding energy of the stabilizing moieties is preferably less than the hybridization energy between the probe sequence and its target sequence;*** (2) the stabilizing moieties are preferably not themselves quenchers; (3) the stabilizing moieties preferably do not interfere with hybridization of the probe to its target sequence; and (4) the stabilizing ligand/oligonucleotide conjugate is preferably cost-effective to manufacture and easily purified. (emphasis added).

Each of these four criteria is readily calculated and/or determined by the skilled practitioner.

Thus, the stabilizing moieties may encompass a wide array of molecules. Significantly, the molecules that function as stabilizing moieties are equivalent and interchangeable provided that the particular molecule(s) meet the four criteria set forth above.

The above discussion covers the substance of the teleconference held on July 29, 2005, between the Examiner and the Examiner's representative, Elizabeth Sampson. As is clear from the above referenced citations to the specification, the subject matter of claims 32-49 was, in fact, clearly and specifically described at the time the application was filed. Thus, the specification discloses the invention in such a way as to reasonably convey that the Applicant had possession of the claimed invention at the time the application was filed. Therefore, Applicant respectfully requests that the rejection 35 U.S.C. §112, first paragraph for alleged inadequate written description be withdrawn.

Under 35 U.S.C. §112, Second Pargraph

Omitted Elements

Claims 50-61 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being incomplete for omitting essential elements, such omission amounting to a gap between the elements for reasons of record set forth in the Office Action mailed November 12, 2004.

Claim 50-61 are now amended to designate the displayed structure as a "probe nucleic acid". Claims 50 and 57 and hence their dependents, are further amended to clarify that when the stabilizing moieties interact to bring the energy donor and acceptor into operative proximity, the probe nucleic acid "is not hybridized to a target nucleic acid."

Thus, the alleged missing elements are now supplied. Therefore Applicant respectfully requests that the rejection under 35 U.S.C. §112, second paragraph, for alleged incompleteness be withdrawn.

Indefiniteness

Claims 32-42 and 44-49 rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to point out and distinctly claim the subject matter that the Applicant regards as the invention.

It is the Examiner's opinion that the phrase "non-nucleic acid" is unclear because it is unclear as to whether the phrase is referring to the fact that the stabilizing moiety does not stabilize nucleic acids, or whether the stabilizing moiety is itself not comprised of a nucleic acid.

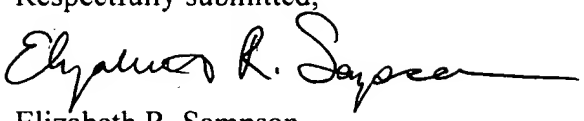
Applicants submit that the discussion above under the rejection for alleged lack of written description under 35 U.S.C. §112, first paragraph, has served to clarify that the phrase "non-nucleic acid" stabilizing moiety, refers to the fact that the stabilizing moiety is itself not a nucleic acid. Therefore, Applicant respectfully requests that the rejection under 35 U.S.C. §112, second paragraph, for alleged indefiniteness be withdrawn.

CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-442-1784.

Respectfully submitted,



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